

Pregnancy and reproductive history may impact dementia risk

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Research reported at the Alzheimer's Association International Conference (AAIC) 2018 in Chicago highlighted sex differences associated with dementia and Alzheimer's disease across the life course,



including the first ever large-scale study of reproductive history and dementia risk in women.

New results reported at AAIC 2018 suggest:

- Associations between <u>dementia</u> risk and number of children, number of miscarriages, age at first menstrual period, and reproductive period (years between first menstrual period and menopause).
- In a separate study, a correlation between cumulative months of pregnancy and Alzheimer's risk.
- Re-thinking the long held thought that hormone therapy negatively affects cognition.
- A need for sex-based standards for cognitive assessments, to improve early detection in women.

"More women than men have Alzheimer's disease or other dementias; almost two-thirds of Americans with Alzheimer's are women," said Maria Carrillo, Ph.D., Alzheimer's Association Chief Science Officer. According to Alzheimer's Association 2018 Alzheimer's Disease Facts and Figures, of the 5.5 million people age 65 or older with Alzheimer's in the United States, 3.4 million are women and 2.0 million are men.

There are a number of potential biological and social reasons why more women than men have Alzheimer's or other dementias. The prevailing view has been that women live longer than men on average, and older age is the greatest risk factor for Alzheimer's. However, some research suggests that the risk for developing Alzheimer's could be greater for women due to biological or genetic variations, or even different life experiences, such as education, occupation or rates of heart disease.

"More research is needed in this area, because having a better understanding of sex-specific risk factors across the lifespan may help us



discover—and eventually apply—specific prevention strategies for different populations of people with Alzheimer's and other dementias," Carrillo added.

Link Between Reproductive History and Dementia Risk in Women

As reported at AAIC 2018, in the first-ever large-scale epidemiological investigation in the U.S. of various aspects of reproductive history and dementia risk, Paola Gilsanz, ScD, staff scientist, Kaiser Permanente Northern California Division of Research in Oakland, Calif.; Rachel Whitmer Ph.D., Professor at UC Davis; and colleagues found a correlation between risk of dementia and the number of children, number of miscarriages, age at the time of first menstrual period, age at natural menopause, and reproductive period (the number of years between first menstrual period and menopause). Self-reported data from 14,595 women between the ages of 40-55 in 1964-1973 were evaluated.

"Possible causes of dementia in women, in particular reproductive factors, are not well understood," said Gilsanz. "In our study, we aimed to identify female-specific risks and protective factors impacting brain health, which is critical to diminishing the disproportionate burden of dementia experienced by women."

The researchers found that women in the study with three or more children had a 12 percent lower risk of dementia compared to women with one child. These women continued to be at lower risk of dementia after adjusting for additional mid- and late-life risk factors, such as body mass index and stroke history.

The researchers also asked about miscarriage and menstrual history. They found that each additional report of a miscarriage was associated



with a 9 percent increased risk of dementia, compared to those women who reported no miscarriages. On average, women were 13 when they had their first menstrual period and were 47 at natural menopause. Additionally, women who indicated having their first menstrual period at age 16 or older were at 31 percent greater risk than those who reported having their first menstrual period at 13. Compared to women who experience natural menopause after age 45, those who experience natural menopause at 45 or younger were at 28% greater dementia risk adjusting for demographics.

The average length of reproductive period was 34 years. Compared to women with reproductive periods of 38-44 years, women with reproductive periods of 21-30 years were at 33% elevated dementia risk adjusting for demographics. Further research is needed to evaluate the mechanistic pathway between reproductive events and brain health.

Women's Pregnancy History May Influence Alzheimer's Risk

(Note: Includes late-breaking analyses generated since the original abstract was submitted in February.)

In a case-control, cross-sectional study of 133 elderly British women, Molly Fox, Ph.D., Assistant Professor, Departments of Anthropology and Psychiatry & Biobehavioral Sciences, University of California, Los Angeles, and colleagues collected reproductive history information and measured severity of Alzheimer's disease dementia to evaluate the potential association between pregnancy history and Alzheimer's risk, and to determine whether the relationship could be attributed to immune function.

Study findings suggest that the number of months of



pregnancy—especially months spent in the first trimester—is a significant predictor of Alzheimer's risk. The researchers report that, in this study population, a woman who spent 12.5 percent more months pregnant than another otherwise identical woman had approximately 20 percent lower Alzheimer's risk.

"We are intrigued by the possibility that pregnancy may reorganize the mother's body in ways that could protect her against developing Alzheimer's later in life," said Fox. "These results also suggest that the story might not be so simple as being all about estrogen exposure, as previous researchers have suggested."

Investigators hypothesized that persisting beneficial effects on the immune system generated during the early stages of pregnancy may be responsible for the observed risk reduction.

Hormone Therapy May Not Always Be Associated with Cognitive Harm

A new study reported at AAIC 2018 sought to investigate why results from the influential Women's Health Initiative-Memory Study (WHIMS) and WHI-Study of Cognitive Aging (WHISCA) differed from previous findings that suggest a worsening of cognition associated with hormone therapy.

Carey E. Gleason, Ph.D., Wisconsin Alzheimer's Disease Research Center, University of Wisconsin School of Medicine and Public Health, Madison, and researchers from Hartford Hospital, Hartford and George Washington University, D.C., looked at two separate studies published since WHIMS and WHISCA: the Kronos Early Estrogen Prevention Study-Cognitive and Affective Study (KEEPS-Cogs); and the Early v. Late Intervention Trial with Estradiol-Cognitive Endpoints (ELITE-



Cog). The results showed:

- No negative effect on cognition was measured in women who had initiated hormone therapy between ages 50-54. In contrast, those who initiated hormone therapy between ages 65-79 demonstrated reductions in global cognition, working memory and executive functioning.
- Women on hormone therapy with type 2 diabetes also showed a higher risk of cognitive impairment compared to non-diabetic women on <u>hormone therapy</u> and diabetic women who were administered placebo treatment, after controlling for age.

"These findings add to our understanding of the complex effects of hormones on the brain," said Gleason. "These data are sorely needed to guide women's healthcare during and after the menopausal transition and to help women make personalized and informed decisions regarding management of their menopausal symptoms and the prevention of future adverse health outcomes."

Female Advantage in Verbal Memory May Mask Early Stages of Alzheimer's

Pauline Maki, Ph.D., Professor of Psychiatry and Psychology, Senior Research Director of the Center for Research on Women and Gender, University of Illinois, Chicago, and researchers from the University of California, San Diego, examined data from the Alzheimer's Disease Neuroimaging Initiative that suggest women have an advantage in retaining memory for words and verbal items, not only during normal aging but also during amnestic mild cognitive impairment (aMCI).

As the tests most frequently used to diagnose Alzheimer's disease are related to <u>verbal memory</u>, memory of word lists, stories and other verbal



materials, researchers wanted to better understand sex differences in verbal memory and brain aging and how they may be related to sex differences in presentation and clinical course of Alzheimer's disease.

The study found that women appeared to sustain their cognitive performance in early stages of disease, compared to men, despite having moderate levels of Alzheimer's brain pathology—as measured by three brain markers (hippocampal atrophy, brain hypometabolism and cortical beta-amyloid deposition). However, at high levels of disease burden, the female advantage in verbal memory was eliminated.

"These findings may help to explain why women show a more rapid decline across a wide range of cognitive abilities after being diagnosed with Alzheimer's," said Maki. "While the female advantage may be functionally beneficial, it could mask early stages of Alzheimer's, resulting in a more severe burden of disease at the time of diagnosis, with more rapid deterioration thereafter."

When a gender-based diagnostic approach was applied, it resulted in improved diagnostic accuracy in both sexes. This suggests the need for, and value of, alternative approaches—such as sex-specific ?cut points? in diagnostic tests—to improve early detection in <u>women</u>.

Provided by Alzheimer's Association

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